Remarks

Telephonic interview

Applicants wish to thank Examiner for granting a telephonic interview after the final office action.

Rejections under 35 USC § 112, first paragraph

Claims 1, 3-5 and 8 stand rejected and claims 21 and 22 are rejected for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. To summarize, The examiner contends that "even in light of narrowing of claim language by reciting specific method steps the claims are still broadly drawn to reprogramming any human somatic cell into a pluripotent cell by administering to said cell an agent which promotes cellular reprogramming," (page 4, last paragraph of detailed action). The stated basis of this rejection is that although "the agents affect gene expression, ... there is no indication that the gene expression correlates with a specific cell type or cell status," (page 6, last line of first paragraph of detailed action). The applicants present evidence in the form of a declaration under 37 CFR § 1.132 and Exhibits 1 and 2, which are incorporated herein by reference, which demonstrate that a keratinocyte treated according the three step protocol described in the specification expresses the pluripotent stem cell markers Oct-4, telomerase and SSEA-1 (see instant specification page 2, lines 15-18 and lines 25-28, and page 3, lines 1-4). This evidence, in view of the state-of-the-art at the time of filing the instant application, would enable the skilled cell biologist to reasonably expect the "reprogrammed" keratinocytes to be pluripotent stem cells.

Claims 1 and 8 have been amended. In order to facilitate prosecution of the present case and not meaning to disclaim any subject matter (said subject matter may be pursued in another patent application), Claim 1 has been amended to be drawn to a method of producing a human pluripotent stem cell from a keratinocyte. This amendment does not present new matter since support for using a keratinocyte as an adult somatic cell in the practice of this invention can be found in original claims 5-8 and Example 2 of the application-as-filed.

Claim 1 has also been amended to include, along with telomerase, the Oct-4 gene product as a molecular marker that is produced by the keratinocyte-derived pluripotent stem cells. Support for including Oct-4 as a claim element, which represents the status of the reprogrammed somatic cell as an embryonic stem cell-like cell, can be found at least at page 24, line32 – line 2, page 25. The purpose of the amendment is to include a claim element that stipulates a specific molecular marker, which the skilled cell biologist would associate only with a pluripotent stem cell. Support for the actual expression of Oct-4 by the reprogrammed keratinocytes/ pluripotent stem cells can be found in the accompanying declaration of Inventor (see section 11 of that declaration) and the accompanying EXHIBIT 2. It is important to note that the RT-PCR experiments and ensuing results presented in EXHIBIT 2, were performed according to the method described in Example 4 of the instant specification using material extracted from keratinocytes that were treated according to the method exactly set forth in Example 2 of the instant specification.

As mentioned above, a major component of the enablement rejection is based upon The examiner's doubt as to whether pluripotent stem cells were actually generated from somatic cells (*i.e.,* keratinocyte) using the claimed method. To provide additional evidence that the reprogrammed keratinocytes of the instant

invention are reasonably expected to be pluripotent stem cells, Inventor's declaration pursuant to 37 CFR § 1.132 and accompanying exhibits EXHIBIT 1 and EXHIBIT 2 are appended herewith and incorporated herein by reference. In that declaration, Inventor has demonstrated that keratinocytes, which were remodeled according to the claimed three step process of treatment described in Example 2, express Oct-4 mRNA (EXHIBIT 2, Figure 2) and SSEA-1 protein (EXHIBIT 1, Figure 1). These particular molecular markers have heretofore only been found to be associated with embryonic germ cells or embryonic stem cells (see specification, page 2, lines 17-18.). Taken together, the in vitro remodeled keratinocytes express known pluripotent stem cell markers telomerase, Oct-4 and SSEA-1. Interestingly, upon subsequent treatment of the instant keratinocyte-derived pluripotent stem cells, expression of SSEA-1 increased above pre-retinoic acid levels. This expression profile of SSEA-1 parallels almost exactly the expression pattern of human embryonic stem cells before and after treatment with retinoic acid (for example see Henderson et al., page 331, Figure 1B). The evidence presented in the declaration and exhibits 1 and 2 demonstrates that the claimed invention is certainly workable and not a "vague intimation of [a] general idea."

Therefore, in view of the evidence, discussion and amendments presented above, which demonstrate that the claimed method of reprogramming keratinocytes results in a cell that expresses at least telomerase, Oct-4 and SSEA-1, which are all pluripotent stem cell markers, The applicants request that the written description/enablement rejection of claims 1-9 under 35 USC 112, first paragraph be withdrawn and the claims allowed.

Rejection under 35 U.S.C. § 112, second paragraph

The claims 1, 3–5, 8, 21 and 22 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The examiner bases this rejection on the alleged lack of clarity in establishing a "relationship of telomerase expression to practicing the method and its relationship to a resulting cell," that resulting cell being a pluripotent stem cell (page 8, lines 2-3 of last paragraph of detailed action). The crux of the examiner's argument is that immortalized and transformed cells also may express telomerase, and that "[telomerase] activity alone is not indicative of a pluripotent cell," (page 8, last line to page 9, first line of detailed action).

Claim 1 has been amended to be drawn to a method of producing a pluripotent stem cell that expresses telomerase and Oct-4, a combination of molecular markers heretofore known only to be expressed in pluripotent stem cells. Furthermore, claim 1 (and claim 8 in a similar manner) has been amended to include the element that the produced pluripotent stem cell has the capability of expressing gene products found in cell types unrelated to each other and the starting keratinocyte, which is also a hallmark of pluripotent cells. Support for the neurofilament, cardiac actin and alpha-antitrypsin language in claims 1 and 8 can be found in working sxample 4 at page 34, lines 15-21.

Claim 4 has been amended to more clearly state that the 5-aza-2′ deoxycytidine, trichostatin A and Tat-cyclin B are the first agent, second agent and third agent respectively.

In view of the clarifying amendments to claims 1, 4 and 8, the applicants request the withdrawal of the rejection of the claims under the second paragraph of 35 USC Section 112.

Rejection under 35 U.S.C. § 102(b)

Applicants gratefully acknowledge Examiner's withdrawal of the reject of claims 1, 3 and 4 under 35 USC § 102(b).

Conclusion

In view of the amendments, evidence and arguments set forth in this response to the Office Action of paper no. 16, the applicants believe that the claims are in condition for allowance. The applicants respectfully request that the rejection of the claims be withdrawn and the claims be allowed to issue. If any outstanding issues remain, Examiner is invited to call undersigned Applicant at the number provided to facilitate the efficient prosecution of this case.

Respectfully submitted,

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